REMARKS

Claims 1, 3, 4, 5, 14, 21 and 22 are pending and under consideration after entry of the amendments set forth herein. Claim 13 is canceled. Claim 22 is added. Support for this claim may be found in the specification, page 8, lines 14-15 and lines 19-20. Claim 1 is amended. Support for these amendments is found in Claim 2 as originally filed, and in the specification, page 14, line 27 through page 15, line 5. No new matter is added.

OBJECTIONS TO THE CLAIMS

Claim 13 is objected for being in the wrong status. Claim 13 currently has a withdrawn status, even though it was examined in the last Office Action (12/31/2007). The Applicants thank the Examiner for pointing out this oversight. The Applicants have canceled Claim 13 herein, rendering this objection moot.

REJECTIONS UNDER §112, ¶2

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Applicants have canceled Claim 13 herein, rendering this rejection moot.

REJECTIONS UNDER §102

Claims 1, 5, 14 and 21, are rejected under 35 U.S.C. 102(b) as anticipated by Wright *et al.* (US PGPB 20020016327 A1, dated 2/7/02).

In making this rejection, the Office Action asserts that" Wright *et al.* teach the treatment of neurogenic inflammation caused by a condition such as radiation induced pain, or radiation burns, by administration of pharmaceutical compositions comprising NSAIDs." (p. 5, l. 12-14).

Newly amended Claim 1 recites a method comprising "contacting said individual with a dose of a non-steroidal anti-inflammatory drug (NSAID) effective to reduce neuroinflammatory activity by recruitment or activation of monocyte/microglial cells; *wherein said loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation in an individual is reduced.*" (emphasis added). The specification teaches that "Cranial radiation can cause a progressive decline in cognition that is linked to long-term ablation of hippocampal neurogenesis" (p. 8, l. 14-15), and that "Cranial irradiation increases the production of pro-

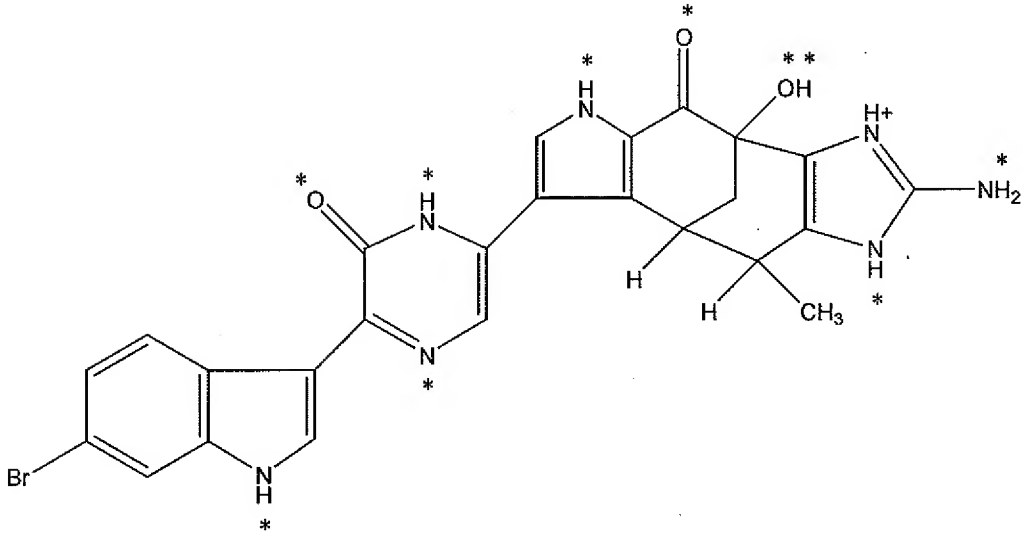
inflammatory cytokines and chemokines in the brains of both mice and men, in particular the production of MCP-1; IL-6; and TNF-α." (p. 8, l. 17-19). It is well understood in the art that the brain is a component of the central nervous system. Thus, the neuroinflammatory effect of cranial irradiation is within the central nervous system.

The Applicants submit that Wright *et al.* do not teach the element of cranial irradiation, or neuroinflammation due to cranial irradiation, or the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation. Accordingly, Wright *et al.* do not teach the pending claims.

Furthermore, the Applicants submit that Wright *et al.* also do not make obvious the pending claims because Wright et al. do not teach treating inflammation of the central nervous system. The Examiner asserts that "Wright *et al.* teach the treatment of neurogenic inflammation caused by conditions like radiation induced pain or radiation burns, by administration of pharmaceutical compositions comprising NSAIDs, e.g. indomethacin along with other antineurogenic inflammatory compounds (para 0012, 0080)." (p. 5, para. 16). Richardson *et al.* ((2002) J Pharmacol Exp Ther. 302(3):839-845) (Exhibit A) teach that neurogenic inflammation is "inflammatory symptoms that result from the release of substances from primary sensory nerve terminals." (col. 2, l. 4-7) Accordingly, neurogenic inflammation is inflammation in the peripheral nervous system. Because Wright *et al.* teach the treatment of inflammation of the peripheral nervous system, Wright *et al.* do not make obvious the pending claims which relate strictly to the central nervous system and specifically to the brain.

Additionally, Wright et al. do not make obvious the pending claims because Wright et al. do not teach compounds that cross the blood brain barrier. Pardridge ((2005) NeuroRx 2:3-14) (Exhibit C), in a review of the art, teaches that "Small molecules generally cross the BBB [Blood-Brain Barrier] in pharmacologically significant amounts if 1) the molecular mass of the drug is less than 400-500 Da, and 2) the drug forms less than 8-10 hydrogen bonds with solvent water." (p. 5, col. 1, l. 15-18) With regard to the latter point, Pardridge further teaches that "It does not matter whether the functional group is a hydrogen bond donor or a hydrogen bond acceptor because each hydrogen bond carries equal weight. Hydrogen bond donor groups such as hydroxyls form two hydrogen bonds because a hydroxyl group acts as both a hydrogen bond donor and hydrogen bond acceptor, whereas a carbonyl group only acts as a hydrogen bond acceptor." (p. 5, col. 1, l. 43-50) Structure II of Wright *et al.* (p. 2, col. 2, l. 5, reproduced below), has 10 opportunities for hydrogen bond acceptance or donation (see asterisks), and the sum of

the atomic weights of the atoms of this compound (24 carbon, 7 nitrogen, 2, oxygen, 20 hydrogen, 1 bromine) is 517.9 Da:



By the same calculation, the compound represented by Structure IV (p. 3, col 1, l. 1) has 12 hydrogen bonds and an atomic weight of 554 Da, and the compound represent by Structure VI (p. 3, col. 2, l. 1) has 9 hydrogen bonds, and an atomic wieght of 517.9 Da. Thus, none of the compounds taught by Wright are less than 500 Da, and none forms less than 9 hydrogen bonds with water. Accordingly, as taught by Pardridge, it is unlikely that the compounds taught by Wright *et al.* can cross the blood brain barrier. In view of this, it would not be obvious to one of ordinary skill in the art to use the compounds of Wright et al. to reduce loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation, as taught by the pending claims.

Thus, Wright *et al.* do not teach or make obvious the pending claims. Withdrawal of the rejection is respectfully requested.

REJECTIONS UNDER §103(A)

Claims 1, 3-5, 13, 14 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sonis et al (US PGPB 20010011097 A1, dated 8/2/01), in view of Ferencik *et al.* (Bratisl Lek Listy 102(3): 123-32, 2001), as evidenced by Price *et al.* (J Med Primatology 30: 81-87, 2001).

The Office Action asserts that Sonis *et al.* teach treating, inhibiting or preventing mucositis in the human cancer patient with head and neck tumors undergoing radiation therapy"

(p. 7, para. 19), but that "Sonis *et al.* do not teach the effect of NSAID on inflammation in the CNS." (p. 7, para. 20)

Newly amended Claim 1 recites a method comprising "contacting said individual with a dose of a non-steroidal anti-inflammatory drug (NSAID) effective to reduce neuroinflammatory activity by recruitment or activation of monocyte/microglial cells; wherein said loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation in an individual is reduced."

The Applicants submit that Sonis *et al.* do not teach cranial irradiation. Accordingly, Sonis *et al.* do not teach neuroinflammation due to cranial irradiation, or the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation, or the use of NSAIDs to reduce loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation.

The Applicants submit that Ferencik *et al.* do not remedy the deficiencies of Sonis *et al.*, because Ferencik *et al.* do not teach cranial irradiation, or neuroinflammation due to cranial irradiation, or the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation, or the use of NSAIDs to reduce the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation.

In making this rejection, the Office Action asserts that "Ferencik *et al.* teach that long-term administration of NSAIDs in subjects with Alzheimer's Disease (AD) and senile dementia, result in a protective effect on the onset of AD and slows down the progression of the disease . . . It is a well established fact that neurodegenerative diseases like AD and dementia are associated with progressive loss of neurogenesis in the central nervous system . . . It would have been therefore obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of treating neuroinflammation and reducing loss of neurogenesis using indomethacin in neurodegenerative disease as taught by Ferencik *et al.*" (p. 7, paragraphs 21-22)

The Applicants submit that, contrary to the Office Action's assertion, it was not known in the art at the time of the invention if Alzheimer's disease (AD) was associated with a progressive loss of <u>neurogenesis</u> (i.e. differentiation of new neurons from progenitor cells) or merely progressive loss of <u>neurons</u>. Indeed, Jin *et al.* ((2004) PNAS 101(36):13363-13367) (Exhibit B) teach that neurogenesis is <u>enhanced</u> in a mouse model of AD (Figures 2 and 3), thus teaching away from the loss of neurogenesis capacity due to AD. Accordingly, the Applicants

submit that one of ordinary skill in the art following the teachings of Ferencik *et al.* would not have predicted that treatment of AD with NSAIDs would impact the capacity for neurogenesis with any measure of success. Likewise, it would not have been obvious to one of skill in the art to consider the use of NSAIDs to reduce the loss of neurogenesis capacity resulting from neuroinflammation due to any other condition or treatment, including cranial irradiation, either. Thus, because Ferencik *et al.* do not teach cranial inflammation, or neuroinflammation due to cranial irradiation, or the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation, or the use of NSAIDs to reduce the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradation, Ferencik *et al.* do not remedy the deficiencies of Sonis *et al.*

The Applicants submit that Price *et al.* do not provide sufficient evidence to remedy the deficiencies of Sonis *et al.* in view of Ferencik *et al.* Price *et al.* teach neuroinflammation from irradiation. Claim 1 recites "contacting said individual *with a dose of a non-steroidal anti-inflammatory drug (NSAID) effective to reduce neuroinflammatory activity* by recruitment or activation of monocyte/microglial cells; wherein said loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation in an individual is reduced." Price teaches neuroinflammation in response to cranial irradiation. However, Price *et al.* do not teach if the neuroinflammation induced by irradiation would be responsive to NSAIDs, and more importantly, if the loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation would be responsive to NSAIDs.

In view of the above remarks, Applicants submit that Sonis *et al.* in view of Ferencik *et al.* as evidenced by Price *et al.* do not make obvious the pending claims. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-303.

Respectfully submitted,
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Date: January 26, 2009

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